



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Luo et al.

Application No.: 09/420,092

Filed: October 18, 1999

For: CELL CYCLE PROTEINS  
ASSOCIATED WITH PCNA,  
COMPOSITIONS AND METHODS OF  
USE

Customer No.: 20350

Confirmation No. 2328

Examiner: Michele Flood

Technology Center/Art Unit: 1654

DECLARATION OF DR. YASUMICHI  
HITOSHI UNDER 37 C.F.R. §1.132

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Yasumichi Hitoshi, M.D., Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.
2. I received my medical degree from Kumamoto University Medical School in 1987. I received a Ph.D. in immunology from The Institute for Medical Science, Kumamoto University Medical School in 1991. I was a postgraduate research associate at the Institute for Medical Immunology, Kumamoto University Medical School in 1991 and at the Institute of Medical Science, The University of Tokyo from 1992-1995. From 1995-1998 I was a postdoctoral fellow in the Department of Molecular Pharmacology at Stanford University. A copy of my curriculum vitae is attached hereto as Exhibit B.

**EXHIBIT A**

3. I have worked at Rigel Pharmaceuticals, Inc. since 1998. Currently, I am Director of Oncology at Rigel Pharmaceuticals, Inc.

4. The present invention claims methods to identify bioactive agents that bind to R0101, a cell cycle protein that is associated with certain cancers.

5. I have read and am familiar with the contents of the patent application. In addition, I have read the Office Action, mailed July 28, 2004, received in the present case. It is my understanding that the Examiner believes that the present invention is supported by neither a specific, substantial, and credible asserted utility nor a well established utility as required by the United States Patent Laws. I respectfully disagree. This declaration is provided to demonstrate that, based on the specification, one of skill in the art would immediately recognize a "real world" utility for the cell cycle protein R0101 and methods of identifying bioactive agents that bind to cell cycle protein R0101.

It is also my understanding that the Examiner believes that the specification does not provide adequate description for the claimed invention. I respectfully disagree. This declaration is provided to demonstrate that on reading the specification, those of skill would understand that the inventors were in possession of the claimed invention.

6. As disclosed in the specification, R0101 is a cell cycle protein that has increased expression in certain cancers and is thus associated with certain cancers, *e.g.*, esophageal cancer, breast cancer, uterine cancer, cervical cancer, brain cancer, kidney cancer, and lung cancer. Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize that R0101 is a useful protein and that bioactive agents that bind to R0101 are also useful. For example, one of skill in the art would expect that bioactive agents that bind to a protein known to be overexpressed in certain cancers, as is R0101, would be useful as indicators of expression of the R0101 and therefore as a diagnostic or prognostic indicators of certain cancers.

7. It is my understanding that the Examiner characterizes Yu *et al.*, oncogene 20:484-489 (2001) as a post-filing reference. The inventors of the present application are also authors of the Yu *et al.* reference. The data disclosed in Figures 2A and 2B of the present invention is the same as the data disclosed in Figures 1b and 1c of Yu *et al.* The data disclosed in Figure 3 of the present invention is the same as the data disclosed in Figure 3 of Yu *et al.* The data disclosed in Figure 5 of the present invention is the same as the data disclosed in Figure 5 of Yu *et al.*

8. Based on Figure 5 and the accompanying legend, those of skill would understand that R0101 is overexpressed in certain cancer cells relative to untransformed cells from the same tissue, *e.g.*, breast, uterus, cervix, brain, kidney, lung and esophagus. More information on experimental conditions is not required by those of skill to arrive at this result.

Figure 5 also includes disclosure of control protein expression levels in the same cell types (bottom row, without asterisks). The control protein expression levels do not uniformly correlate with the increases in R0101 expression and thus, the R0101 overexpression in cancer cells is specific to particular cancers and is not merely a result of "an increase in metabolic protein activity" as asserted by the Office Action.

9. Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize R0101 as a useful protein. For example, one of skill in the art would expect that a protein known to be overexpressed in certain cancers, as is R0101, would be useful as a diagnostic or prognostic indicator of those cancers. Furthermore, because R0101 is demonstrated to be overexpressed in certain cancers, *e.g.*, esophageal cancer, and not others, *e.g.*, stomach and colon, R0101 is properly characterized a specific marker of certain cancers rather than a "metabolically active protein", as asserted by the Office Action.

10. Because of the overexpression of R0101 in certain cancers, one of skill in the art would recognize that bioactive agents that bind to R0101 are useful. For example, one of skill in the art would expect that bioactive agents that bind to a protein known to be

overexpressed in certain cancers, as is R0101, would be useful as indicators of expression of the R0101 and therefore as a diagnostic or prognostic indicators of certain cancers.

11. In view of the foregoing, it is my scientific opinion that one of skill in the art, at the time the application was filed, would recognize the real world utility of the claimed methods.

12. It is my understanding that the Examiner believes that the claimed methods of screening for a bioactive agent that binds to protein R0101 are not described in the specification. I respectfully disagree. Based on the specification as filed, those of skill would be able to practice the claimed methods. The specification at page 27, line 32 through page 30, line 32, discloses binding assays where, *e.g.*, R0101 protein is bound to a solid support and a candidate bioactive agent is added. In one example, labeling of the candidate agent is disclosed. *See, e.g.*, page 28, lines 20-33. Excess agent is washed from the R0101 protein and the amount of label is assayed in order to determine whether binding has occurred. Variations of the assays are described, including competitive assays. *See, e.g.*, page 29, line 10 through page 30, line 6. Candidate bioactive agents are described at page 23, line 33 through page 27, line 31. Two hybrid assays are also described at page 39, line 3 through page 40, line 3, and would also be understood by those of skill to be of use the claimed methods. Examples of two-hybrid assays are provided at Figure 8 of the specification. Therefore, based on the disclosure of the specification, those of skill would understand that the inventors were in possession of the claimed invention at the time of filing.

13. In view of the foregoing, it is my scientific opinion that one of skill in the art, at the time the application was filed, would recognize that the inventors were in possession of the claimed methods.

Date: \_\_\_\_\_

7/27/05

By: \_\_\_\_\_

Yasumichi Hitoshi

Yasumichi Hitoshi, M.D., Ph.D.